Murine embryonic stem cell-derived pyramidal neurons integrate into the cerebral cortex and appropriately project axons to subcortical targets.

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Public Summary:

Scientific Abstract:
Although embryonic stem (ES) cells have been induced to differentiate into diverse neuronal cell types, the production of cortical projection neurons with the correct morphology and axonal connectivity has not been demonstrated. Here, we show that in vitro patterning is critical for generating neural precursor cells (ES-NPCs) competent to form cortical pyramidal neurons. During the first week of neural induction, these ES-NPCs begin to express genes that are specific for forebrain progenitors; an additional week of differentiation produces mature neurons with many features of cortical pyramidal neurons. After transplantation into the murine cerebral cortex, these specified ES-NPCs manifest the correct dendritic and axonal connectivity for their areal location. ES-NPCs transplanted into the deep layers of the motor cortex differentiate into layer 5 pyramidal neurons and extend axons to distant subcortical targets such as the pons and as far caudal as the pyramidal decussation and descending spinal tract and, importantly, do not extend axons to inappropriate targets such as the superior colliculus (SC). ES-NPCs transplanted into the visual cortex extend axons to the dorsal aspect of the SC and pons but avoid ventral SC and the pyramidal tract, whereas cells transplanted deep into the somatosensory cortex project axons to the ventral SC, avoiding the dorsal SC. Thus, these data establish that ES-derived cortical projection neurons can integrate into anatomically relevant circuits.